REMARKS

Status of Claims and Amendment

Claims 17, 20-22, 24 and 26 are all the claims pending in the application. Claims 17, 20-22, 24 and 26 are rejected. Upon entry of this Amendment, which is respectfully requested, Claims 17, 24 and 26 will be amended. Claims 20-22 will be canceled.

Support for the amendment to Claim 17 can be found throughout the specification, at least at page 4, lines 6-19, at page 5, lines 25-27, at page 6, lines 1-4, at page 6, lines 12-15, and the last paragraph bridging pages 14 and 15. Support for the amendment to Claim 24 can be found throughout the specification, for example, at page 5, lines 25-27, at page 6, lines 1-4, at page 6, lines 16-19, and the last paragraph bridging pages 14 and 15. Support for the amendment to Claim 20 can be found throughout the specification, at least, at page 4, lines 6-19, at page 5, lines 25-27, at page 6, lines 1-4, at page 6, lines 12-19, and the last paragraph bridging pages 14 and 15.

No new matter is added.

Claim Summary

The Office Action states that claims are under examination with regard to SEQ ID NO: 1 (p24), SEQ ID NO: 3 (p40), and SEQ ID NO: 8 (p10) as a result of the restriction requirement and election of species requirement. The Office Action states that SEQ ID NO: 5, 7, 6, and 8 are not under examination.

In response, Claims 17, 24 and 26 have been amended in order to remove non-elected sequences. Specifically, Claim 17 has been amended to recite SEQ ID NO: 8 (p10) and SEQ ID NO: 1 (p24). Claim 24 has been amended to recite SEQ ID NO: 8 (p10) and SEQ ID NO: 3

(p40). Claim 26 has been amended to recite SEQ ID NO: 8 (p10), SEQ ID NO: 1 (p24) and SEQ ID NO: 3 (p40). Subsequently, Claims 20-22 have been canceled.

Response to Claim Rejections under 35 U.S.C. § 103

In the Office Action, Claims 17, 20-22, 24 and 26 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yamaguchi et al. (*Ann. Clin. Biochem.* 2001, 38:348-355, "Yamaguchi"), in view of Watanabe et al. (*J. Vet. Med. Sci.*, 2000, 62(7):775-778, "Watanabe"), Planz et al. (*Journal of Virology*, 1999, 73:6251-6256, "Planz") and further in view of Hatalski et al. (*Journal of Virology*, February 1995, 69(2):741-747, "Hatalski"), and Carbone, K.M. (*Clin. Micro. Rev.*, 2001, 14(3):513-527, "Carbone").

The Examiner states that one of ordinary skill in the art would have been motivated to utilize anti-p10 antibodies, as well as anti-p40 and anti-p24 antibodies for the purpose of increasing the sensitivity of Yamaguchi's method. Specifically, the Examiner states that Watanabe suggests that antibodies to individual viral proteins and BDV-specific antigens are useful in Yamaguchi's method. The Examiner further states that the motivation to modify Yamaguchi's method comes from the improved diagnostic method that would result from increasing the sensitivity of Yamaguchi's method by detecting anti-p10 antibodies in addition to anti-p24 and anti-p40 antibodies. The Examiner also states that since Hatalski demonstrates that IgM is present in response to BDV infection, and Carbone indicates that IgM is often the first serological evidence of BDV infection, one would have had a reasonable expectation of success that testing for the presence of IgM and IgG would have worked in Yamaguchi's method to increase sensitivity and detect evidence of an infection as early as possible. Accordingly, the Examiner states that the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

In response, Applicants respectfully traverse this rejection for the following reasons.

Applicants note that Watanabe teaches the expression of individual BDV viral proteins including p10. However, Applicants submit that Watanabe essentially fails to teach the motivation to modify Yamaguchi's electrochemiluminescence immunoassay (ECLIA) to include the detection of p10. Furthermore, Watanabe does not teach the detection of both IgM and IgG antibodies in the assay. The Examiner states that the addition of p10 would increase the sensitivity of Yamaguchi's method without providing a reference suggesting motivation to combine or showing a reasonable expectation of success. Applicants note that the validity of a diagnostic test can be determined by measuring the rate of sensitivity (true-negative rate) and specificity (true-positive rate) (Carbone et al., Page 515, Column 2, line 47-50). Accordingly, Applicants submit that it is equally important to improve the specificity of diagnostic tests in order to minimize false positives and thus prevent individuals from getting unnecessary treatment. Additionally, Applicants note that BDV expresses 6 classes of proteins (N,P,M,G,L, and p10) which undergo distinct secondary modifications such as glycosylation and phosphorylation. Applicants also note that the viral proteins form distinct heteromeric complexes (Carbone et al., Page 514, Column 1, line 27-31). Thus, contrary to the Examiner's reasoning, Applicants submit that adding an additional BDV antigen in the diagnostic method might compromise the specificity of the assay unless the antigen is carefully selected by examining its expression profile and the cross reactivity of the antibody raised against the antigen.

With respect to the Hatalski and Carbone references, Applicants submit that neither Hatalski nor Carbone teaches the merits of detecting both IgM and IgG upon BDV infection. In fact, the cited references only disclose the presence of IgM in the serum at the early phase of

BDV infection. Applicants also note that Hatalski discloses the characterization of anti-gp18 monoclonal antibodies (two IgG class and three IgM class) raised specifically against recombinant gp18 protein but not against BDV. Further, the antibody was artificially raised in mice by injecting a large amount of recombinant gp18 proteins. Therefore, Applicants submit that the characteristics of IgM antibodies disclosed in Hatalski can not be compared with the IgM antibodies which are raised in the host in response to BDV infection.

Applicants also submit that Carbone does not teach the use of IgM antibodies in determining infection by BDV. Rather, the reference teaches the detection of anti-BDV IgG antibodies at the convalescent-phase. It is known in the art that IgM antibodies are the first class of antibodies that are made in response to infection (Carbone et al., Page 516, Column 1, line 27-30). However, Applicants also note that most IgM antibodies quickly disappear approximately one month after their appearance and are replaced by IgG antibodies as disclosed in the specification (page 2, the whole 1st paragraph). Thus, the single detection of IgG antibodies is more common in determining infection by BDV since IgM antibodies are thought to be absent in the convalescent phase. Accordingly, Carbone suggests a method of detecting IgG rather than IgM antibodies explaining that it is not always possible to obtain acute phase serum in natural BDV infections (page 516, column 1, line 37-40).

Importantly, the instant specification discloses unexpected results in that it requires an unusually long period of time for the class switching between IgM and IgG antibodies to take place (Page 31, line 1-4). Specifically, Applicants demonstrate that IgM antibodies are detected even one year after BDV infection (page 12, line 17-22). Thus, the unusual property of the IgM antibodies disclosed by Applicants allows one to examine the presence of both IgM and IgG not only at the early phase but also at the later phase of BDV infection. Given the distinct kinetics of

IgM antibodies raised by BDV infection, Applicants submit that it is unlikely that one of ordinary skill in the art would have had a reasonable expectation that testing both IgM and IgG antibodies would increase the sensitivity in detecting an infection absent the knowledge from Applicants' disclosure. Applicants acknowledge that it might be difficult to determine whether a subject is on an active or a cleared state of infection with BDV based upon the detection of the antibodies as disclosed in the present invention. However, contrary to the Examiner's assertion, the objective of the present invention is not determining whether a subject is in an active or a cleared state of BDV infection. Rather, the present invention is directed to "a method for detecting whether a subject has been infected with Borna Disease Virus" as recited in Claims 17, 24 and 26.

Further, Applicants submit that the present invention provides unexpectedly superior results over Yamaguchi's ECLIA method. Applicants submit that Comparative Example 1 of the instant specification demonstrates improvement of BDV detection rate when p10 antibodies are included in the assay in comparison to the method detecting p24 and p40 antigens, e.g., Yamaguchi (pages 22-25, Table 1). Specifically, Table 1 shows that 17 out of 23 specimens (73.9%) are detected as positive for BDV infection when p24 and p40 antibodies are used in the assay. In contrast, the data show that the BDV detection rate increases to 95.7% (22 out of 23 specimens) when p10 antibodies are included in the method. Importantly, 5 out of 23 specimens were detected with p10 antibodies but not with p24 nor with p40 antibodies indicating that the detection of p10 increases the sensitivity of the BDV detection method without compromising the specificity of the assay.

In order to further clarify the claim language, Claims 17, 24 and 26 have been amended to recite "A method for determining whether a subject has been infected with Borna disease virus

(BDV), comprising: " in line 1 and also to recite "wherein said subject is determined to have been infected" in line 10 of Claims 17 and 24 and in line 11 of Claim 26.

In conclusion, Applicants submit that the combined teachings of Watanabe, Hatalski and Carbone fail to provide the motivation to modify Yamaguchi's ECLIA method to include the p10 antibody and to examine both IgM and IgG antibodies in the assay. Furthermore, Applicants submit that the present invention demonstrates unexpected superior results over Yamaguchi's method. Accordingly, in view of foregoing, Applicants submit that the present invention is not obvious over cited references and thus respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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